COMMENTS ON THE REPORT OF GORI DATED OCTOBER 22, 1981 USING SERA COTININE AS AN INDICATOR OF CIGARETTE TAR YIELD AND THE REPORT OF DARBY AND McNAMEE

In our prior submission to the Commission, we indicated that the report by Gori failed to provide information such as number of people involved in the tests, initial plasma cotinine levels, the number of cigarettes smoked, time cigarettes were smoked, variability of results, and correlation between FTC smoke yield and serum cotinine. We were, therefore, unable to evaluate the significance of the results.

In this more recent submission, an additional study has been conducted but Gori still does not provide any data establishing a relationship between FTC machine smoked cigarette tar and nicotine yield and serum cotinine. The reader is simply told that the serum cotinine levels that are reported for Barclay, Cambridge, Carlton, and Now are appropriate in that Barclay delivers .2 mg nicotine and the other brands 0.1 mg nicotine. The B&W submission also includes a report by Darby and McNamee who indicate that their analysis of the pharmokinetics of nicotine and cotinine in the human predicts the results obtained by Gori. We believe that Darby and McNamee's report contains a number of significant errors. First, their equation number 1 on page 4 indicates the half-life of nicotine to be 10 minutes. In Gori's paper and elsewhere in the B&W submissions, the half-life of nicotine is suggested to be 30 minutes. Our own analysis of the literature indicates

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it to be about 40 minutes. In equation 2 on page 5 of the Darby report, the signs seem to be reversed, and the half-life of cotinine in plasma is given as 30 hours. Gori also refers to the half-life of cotinine as being 30 hours. Interestingly, the references cited by Darby on the half-life of cotinine are the 1979 edition of the Surgeon General's Report and a report compiled by the ERF of the American Medical Association. We are unable to find a citation of the half-life of cotinine in either of these references.

Zeidenberg, P. et al. (Comprehensive Psychiatry 18:93, 1977) is sometimes cited for the half-life of cotinine, however, no data is given in the paper, and it is only in the introduction that a 30 hour half-life of cotinine is given (without reference). Gritz, E. R. et al. (Clinical Pharmacology and Therapeutics, Vol. 30, No. 2, page 201, 1981) state the half-life of cotinine as 30 hours (reference: Langone, J. J., et al, Biochemistry, Vol. 12, page 5025, 1973). The Langone reference gives data on two different human subjects. They do not, however, specifically calculate the half-life of cotinine from these data. Using their data, we have estimated the half-life of cotinine in sera to be 19 hours. Interestingly, cotinine data in 24 hour urine samples from these same subjects is given in the paper, and this affords a renal half-life of 30 hours. Langone, et al., Research Communications in Chemical Pathology and Pharmacology, Vol. 10, No. 1, page 21, (1975), also contains one set of data for a single subject on sera

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cotinine decay, and we have again estimated the half-life at about 19 hours in plasma. We conclude that the half-life of plasma cotinine is not 30 hours and that the extremely limited data on humans gives a half-life of serum cotinine of 19 hours.

Neither the Gori report nor the Darby report provide detail on the number of cigarettes smoked by day or the time of day in which they are smoked, and, therefore, we could not precisely duplicate the calculations to determine the error introduced by the use of erroneous values for nicotine and cotinine half-life. However, we did make some assumptions and estimated the effect of changing these parameters. Since the daily average number of cigarettes consumed by the panelists in the two Gori studies combined was about 28, we used this number as the simulated number smoked on each day. The daily smoking simulation started at 8:30 AM and continued at half-hour intervals until 28 cigarettes had been smoked. The time for calculation of the simulated serum cotinine was chosen as 4:30 PM on the seventh day of the smoking regime. Under these conditions, the Darby model and modified model produced the following sera cotinine levels.

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Table 1

Darby Model		Modified Model	
Assumed Amt. of Nicotine Absorbed from Cigarette (mg)	Nicotine half-life (10 min.); Cotinine half-life (1800 min.) Estimated Serum Cotinine (µg/ml)	Assumed Amt. of Nicotine Absorbed from Cigarette (mg)	Nicotine half-life (40 min.); Cotinine half-life (1140 min.) Estimated Serum Cotinine (µg/ml)
.1	90	.1	59
.2	180	.2	118
.3	270	.3	177
.4	360	.4	236

Clearly, these changes in half-life significantly alter the estimated yield from a cigarette when this is to be inferred from the serum cotinine level obtained by Gori and the pharmokinetic model (compare data in Tables I and II).

Table II

Average of all Serum Cotinine Data by Gori

Brand	Cotinine (ng/ml)
Barclay	176
Cambridge	103
Carlton	107
Now	98

The form of the pharmokinetic model proposed by Darby estimates that the level of serum cotinine will increase linearly with the yield of the cigarette providing the same number of cigarettes are smoked at the same times.

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Unfortunately, (as we have previously indicated), no experimental data is provided by Gori to indicate whether or not this is true, and when more appropriate half-lives are included in the model, there is not a 1:1 correspondence between the nominal FTC nicotine yield of the cigarette and the serum cotinine level predicted by the model.

Gori has commented on the design of his experiment where only smokers of the four commercial cigarettes Barclay, Cambridge, Carlton, and Now are used, and they are rotated in a random design among these cigarettes, each for a one week period. Gori states on page 4 of his October 22, 1981 report that smokers of higher tar cigarettes would cause greater variability of results and that their behavior and perhaps smoke metabolism is most likely different from the low-yield smokers, and consequently, the relationship of smoke residues in smokers of high yield cigarettes does not follow a 1:1 proportion, when matched to the nominal FTC yield of the cigarette smoked. Gori also states on page 5 that another experimental approach would be to ask smokers to switch to a higher or lower yield brand and then measure their intake by objective methods. He argues that the results of such an experiment would be distorted by well-known compensatory phenomena which would create great difficulties in interpretation.

To us, this means that Gori believes the cotinine serum level is not directly proportional to the nominal FTC smoke and nicotine yield as nicotine levels of the cigarettes are increased or decreased. This, of course, is

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not the situation represented by the Darby Model.

We agree with these statements by Gori in that they are supported by others. Creighton, D. E. and Lewis, P. H. (Smoking Behavior, Editor Thornton, Churchill-Livingstone, London/New York, page 289, 1978) reported that individuals switched among different yield cigarettes compensated partially or totally for the differences in yields of the cigarettes.

Thus, if Barclay is a higher tar and nicotine yielding cigarette than the others, compensation is to be expected as Barclay is rotated among the smokers. Given this Catch 22 type situation, it is unrealistic for Gori and B&W to consider this limited experiment as definitive.

COMMENTS ON THE REPORT OF GORI DATED OCTOBER 22, 1981 USING EXHALED CARBON MONOXIDE CONCENTRATION AS AN INDICATOR OF CIGARETTE TAR YIELD

In our prior submission to the Commission, we indicated that carbon monoxide content of exhaled breath or the corresponding carboxyhemoglobin level had been used in efforts to distinguish the amount smoked. However, this technique has not been successful due to the lack of an established correlation between smoke intake and carboxy-hemoglobin. The problems arise from the fact that carboxy-hemoglobin has a relatively short and somewhat variable half-life in the human. The half-life variability is introduced in part by the fact that differing ventilation rates would be incurred under completely sedentary and various ranges of activity.

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Gori has used a half-life of five hours, and a diary recording the time that each cigarette was smoked to construct a model for adjusting the carbon monoxide values. We have examined the model as given by his equation at the bottom of page 19 and find that the first term $[CO_m\ (.5)^{(t-t_m)/H}]$ has a relatively small value and contributes only about 10% of the expired carbon monoxide value measured late in the afternoon.

If we assume that cigarettes are smoked beginning at 8:30 AM and continuing at half-hour intervals until 3:30 PM (the approximate time at which Gori indicates he conducted the analysis), the following value results for the second term in his equation:

$$U \sum_{i=1}^{15} .353 + .378 + .406 + .435 + .466 + .500 + .538 + .570 + .615 + .659 + .707 + .758 + .815 + .870 + .933$$

This means that the exhaled carbon monoxide value has little dependence on the prior day's smoking and a decreased dependence on the cigarettes smoked early in the day, or conversely, a high dependence on the last few cigarettes smoked. This, of course, means that there is very little averaging of the smokers' habits and, therefore, high variability of results is to be expected. Gori's data is reflective of this, in that standard errors are frequently found to be 50% of the mean.

Again, Gori fails to provide any information which would suggest that a correlation exists between the FTC carbon monoxide yield of a cigarette and the carbon monoxide

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concentration in the exhaled breath of a smoker. Interpretation of the data is also complicated by possible smoker compensation for higher yielding products in a study such as this where cigarettes are rotated among smokers over a relatively short time period.

We conclude that these data suffer from the same problems as the cotinine measurements and their interpretation, except that the carbon monoxide data are less meaningful because of the shorter half-life, probable greater half-life variability, and high dependence on the last few cigarettes smoked.

COMMENTS ON THE OCTOBER 23, 1981 SUBMISSION BY PAUL, WEISS, RIFKIND, WHARTON & GARRISON ON BEHALF OF BROWN AND WILLIAMSON

On page 24 of this document, Brown & Williamson comments on the September 1, 1981 submission by Lorillard to the FTC. They call the experiment bizarre, apparently on the basis of a lack of correlation between the ratio of tar delivered by a number of Lorillard brands to that delivered by Now and the FTC tar. They depict this data in graphic form on page 25 and label the ordinate "'Smoke in a Bottle' Relative to Now" and the abscissa "Mg 'Tar' Advertized by FTC Method" and give the figure the title "How Some Lorillard Employees Apparently Smoke Lorillard Products". These data represent single cigarettes each smoked by a different individual.

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Creighton, D. E., Noble, M. J., and Whewell, R. T. (Smoking Behavior, Edited by Thornton, Churchill-Livingstone London/New York, 1978, p. 277-300) have reported a device to measure, record, and duplicate human smoking patterns. They recorded human puff volumes, puff velocities, puff intervals, puff numbers, and puff profiles on punch tape, and these were used to program the smoking machine. Tar, nicotine, and carbon monoxide were measured under the various conditions recorded for human smoking which can be compared to the standard conditions used by the FTC. The tar obtained in the oral cavity, as reflected by their smoking patterns, varied from +200% to -80% of the machine value at standard conditions. (Incidentally, this book was edited by a senior scientist from the Group Research and Development Center at BAT, the parent company of Brown and Williamson. B&W scientists were listed as present at the symposium where the papers were originally given.) This means that the ratio for individual brands on single cigarette smokings by individual smokers reported previously by Lorillard and termed bizarre by Brown and Williamson fall generally within the range of variation reported above and is well known to B&W. We conclude that Lorillard employees smoke in a manner similar to BAT employees.

Brown and Williamson's further statement that "according to Lorillard's data, the FTC, to be accurate should adopt a filter holder that obtains higher tar delivery for Kent III cigarettes (3 mg per current FTC method) than for Golden Lights (7 mg), higher tar delivery

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for Golden Lights than for Kents (12 mg), and equivalent tar levels for True (5 mg) and Newport Red (14 mg)" has no meaning, and can only arise from their total misunderstanding of the reported information. We report under Attachment 2 and Table 1 the effect that the PM holder would have on the tar yield of a number of brands. Only the tar yield of Barclay is changed significantly from that obtained with the holder currently used by the FTC.

The major point of the submission under Attachment 1 relates to the relative yield of tar obtained by individual smokers from Carlton, Now, Barclay cigarettes, and their own brand. Each of the individual 20 smokers obtained more tar from the Barclay cigarettes than they did from the Now, and frequently the amount obtained from the Barclay was as high as that obtained from their regular Lorillard brand. Additionally when we average the ratios obtained from the twenty smokers on Carlton, Now and Barclay cigarettes, we report that the Barclay delivers about four times as much tar to the smoker's oral cavity as the Now and 3.3 times as much as the Carlton. These data correlate well with the higher taste levels associated with Barclay by R. J. Reynolds' submission and Lorillard's own taste panel data. They also agree with the data submitted in the Philip Morris butt study.

We believe that the Lorillard data result from a direct measure of the relative amount of tar delivered by Barclay cigarettes to a random group of smokers with respect to the tar level of their regular brand. No

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assumptions are made concerning the ratio of tar to other smoke components as in the butt studies and the Gori experiments.

COMMENTS ON THE TECHNICAL APPENDIX DATED OCTOBER 23, 1981 ACCOMPANYING THE SUBMISSION TO THE FTC ON BEHALF OF BROWN AND WILLIAMSON

We find this material somewhat confusing, particularly if the reader does not have a thorough understanding of the dependence of tar and other smoke components on the smoking parameters. For example, Brown and Williamson on page 9, Figure B, indicates that puff volume has a greater effect on retained nicotine than does velocity. Although true, the question is "Is there a relationship between puff volume and the retention efficiency of the filter?" The answer to that question is "No". The retention characteristics of the filter do change with smoke velocity as previously pointed out by Lorillard and Philip Morris. The assumption inherent in any butt study is that the filtration efficiency of the filter must be assumed as a constant. The principal variable affecting filtration efficiency is smoke velocity. The construction of the Barclay filter is such that smoke velocity through the filter under FTC smoking conditions is very low (with approximately 80% ventilation behind the filter). Occlusion of the air channels at constant puff volume and duration alters smoke velocity through the filter, and filtration efficiency drops significantly (as pointed out in Lorillard's earlier submission).

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Thus, it is impossible to consider a butt study valid with this type cigarette unless the dilution under human smoking conditions is known. We have also pointed out previously that the relationship between filtration efficiency and smoke velocity is exponential, and a 50% increase in velocity (for example, a combination of decreased ventilation and increased puff volume of constant duration) produces a rather dramatic effect on the tar delivered. This could easily account for the results obtained by Lorillard in the study reporting data on the delivery of Barclay to human volunteers.

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